



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(54) Title: 3-(AMINO- OR AMINOALKYL)PYRIDINONE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF HIV RELATED DISEASES</p> <p>(57) Abstract</p> <p>The present invention is concerned with 3-(amino- or aminoalkyl)pyridinone derivatives which inhibit the reverse transcriptase of the Human Immunodeficiency Virus (HIV). It relates moreover to the use of such compounds for treating HIV-related diseases. Furthermore it relates to a process for the preparation of these compounds.</p> <p style="text-align: right;">69 + 158 → 15 for any 1?</p>		

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3-(Amino- or aminoalkyl)pyridinone derivatives and their  
use for the treatment of HIV related diseases

The present invention is concerned with 3-(amino- or aminoalkyl)  
pyridinone derivatives which inhibit the reverse transcriptase of the Human  
Immunodeficiency Virus (HIV).

It relates moreover to the use of such compounds for treating HIV-  
5 related diseases.

Furthermore it relates to a process for the preparation of these  
compounds.

It is known that some pyrimidinone and pyridinone derivatives  
inhibit HIV reverse transcriptase.

10 In particular, derivatives from 1-[(2-hydroxyethoxy)methyl]-6-  
(phenylthio)thymine (HEPT) are well known for their HIV1 reverse  
transcriptase inhibitory properties.

European Patent Application EP-0 462 800 (Merck and Company  
Inc.) discloses pyridinones being substituted on position 3 with an aryl or  
15 heterocyclic group, linked to the pyridinone ring through a chain.

Unfortunately, strains resistant to these compounds appeared .  
Thus, their use in therapeutical treatments is questionable.

4-aryl-thio-pyridinones have been more recently disclosed by  
DOLLE et al. (1995, J. Med. Chem., 38, 4679-4686), and in the  
20 corresponding PCT Patent Application WO 97/05 113.

However, their activities are still moderate and their use in human  
therapy also could lead to the emergence of resistant strains.

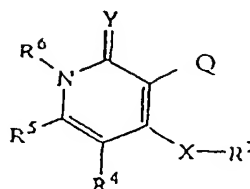
The most active thio pyridinones disclosed therein have a 50%  
inhibitory concentration of virus multiplication ( $IC_{50}$ ) for nevirapine resistant  
25 strains of about 260 nM.

The inventors have found a new pyridinone derivative family which  
show better HIV inhibitory properties.

They have moreover found a new process for obtaining these  
compounds.

The present invention relates to compounds having the following general formula I.

FORMULA (I)



wherein

- Q represents  $-NR_1R_2$  or  $-R_0NR_1R_2$  wherein:

\*  $R_0$  represents  $C_{1-6}$  alkanediyl;

\*  $R_1$  and  $R_2$  each independently represent  $C_{1-6}$ alkyl or  $C_{3-6}$ alkenyl;

15 said  $C_{1-6}$ alkyl and  $C_{3-6}$ alkenyl may be substituted with one, two or three substituents selected from hydroxy,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkylthio, aryloxy, arylthio, amino, mono- or di( $C_{1-4}$ alkyl)amino and aryl; or

\*  $R_1$  and  $R_2$  taken together may form a bivalent radical  $-R_1-R_2-$  wherein  $-R_1-R_2-$  represents  $-(CH_2)_2-O-(CH_2)_2-$ ,  $-(CH_2)_2-NR_7-(CH_2)_2-$ ,

20  $-(CH_2)_2-CH(NHR_7)-(CH_2)_2-$  or  $-(CH_2)_n$ , wherein  $R_7$  represents hydrogen or  $C_{1-4}$ alkyl and  $n$  represents 2, 3, 4, 5 or 6;

-  $R_3$  represents aryl or a monocyclic or bicyclic heterocycle selected from pyridinyl, pyrimidinyl, thiazolinyl, furanyl, thienyl, imidazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl; said monocyclic or bicyclic  
25 heterocycle may optionally be substituted with one, two or three substituents each independently selected from hydroxy,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, halo, trifluoromethyl, dimethylenoxy or phenyl,

-  $R_4$  and  $R_5$  each independently represent hydrogen,  $C_{1-6}$ alkyl,  $C_{3-6}$ alkenyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkyl, amino, mono- or di( $C_{1-4}$ alkyl)  
30 amino, formyl,  $C_{1-4}$ alkylcarbonyl, carboxyl,  $C_{1-4}$ alkyloxycarbonyl, or  $C_{1-4}$ alkyl-

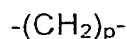
aminocarbonyl; wherein C<sub>1-6</sub>alkyl and C<sub>3-6</sub>alkenyl may be substituted with one, two or three substituents selected from hydroxy, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkylthio, aryloxy, arylthio, amino, mono- or di(C<sub>1-4</sub>alkyl)amino and aryl; or

- R<sub>4</sub> and R<sub>5</sub> taken together form a bivalent radical of formula -R<sub>4</sub>-R<sub>5</sub>- wherein -R<sub>4</sub>.R<sub>5</sub>- represents -CH=CH-CH=CH- or -(CH<sub>2</sub>)<sub>t</sub>-, wherein t represents 3 or 4;

- R<sub>6</sub> represents hydrogen, hydroxy, C<sub>1-4</sub>alkyloxy, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, aryl, C<sub>1-4</sub>alkyl, amino, mono- or di(C<sub>1-4</sub>alkyl)amino or alkylaryl;

- Y represents O or S;

- X represents a radical of formula:



wherein p represents 1, 2, 3, 4 or 5;

q represents 0, 1, 2, 3, 4 or 5;

r represents 0, 1, 2 or 3;

- Z represents NR<sub>8</sub>, C(=O), CHOH, CHNR<sub>8</sub>R<sub>9</sub>, CF<sub>2</sub>, O, S or CH=CH; wherein R<sub>8</sub> and R<sub>9</sub> each independently represent hydrogen or C<sub>1-4</sub>alkyl;

or

N-oxides, stereochemically isomeric forms or a pharmaceutically acceptable addition salts thereof.

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C<sub>1-4</sub>-alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, butyl and the like; C<sub>1-6</sub>alkyl is meant to include C<sub>1-4</sub>alkyl and the higher homologues thereof containing 5 to 6 carbon atoms such as, for example, pentyl, hexyl or the like; C<sub>3-6</sub>alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms, such as 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl and the like; and the carbon atom

of said C<sub>3-6</sub>alkenyl being connected to a nitrogen atom preferably is saturated; C<sub>1-6</sub>alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 5 1,6-hexanediyl and the like. The term «C(=O)» refers to a carbonyl group. Aryl is phenyl or phenyl substituted with one, two or three substituents selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxy, halo and trifluoromethyl,

Preferred compounds according to the present invention are those in which X represents -CH<sub>2</sub>- or C (= O) and R<sub>3</sub> represents a phenyl group, 10 substituted with two methyl groups, and the most preferred of them are those wherein R<sub>3</sub> represents a phenyl group substituted, in each meta position, with two methyl groups.

Preferably, in the compounds according to the present invention, R<sub>1</sub> and R<sub>2</sub> represent each a methyl group, R<sub>4</sub> represents an ethyl group, R<sub>5</sub> 15 represents a methyl group and/or R<sub>6</sub> represents a hydrogen atom.

The most preferred compound of this invention is the 3-dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one.

The compounds in which X is -CH<sub>2</sub>-, R<sub>3</sub> represents a phenyl group optionally substituted, Y represents O and R<sub>6</sub> represents a hydrogen atom 20 can be obtained by the general process represented on figure 1.

This first process comprises the following steps:

a) reacting a pyridine (2), substituted in position 2 with an alkoxy group and in position 3 with an amidoalkyl group, with a C<sub>1</sub>-C<sub>6</sub> alkyllithium, resulting in a lithiated derivate (3) of the said pyridine.

25 b) transforming the lithiated derivate (3) into an organocopper reagent by reacting it with a complex formed by Cu I and dimethyl sulphide.

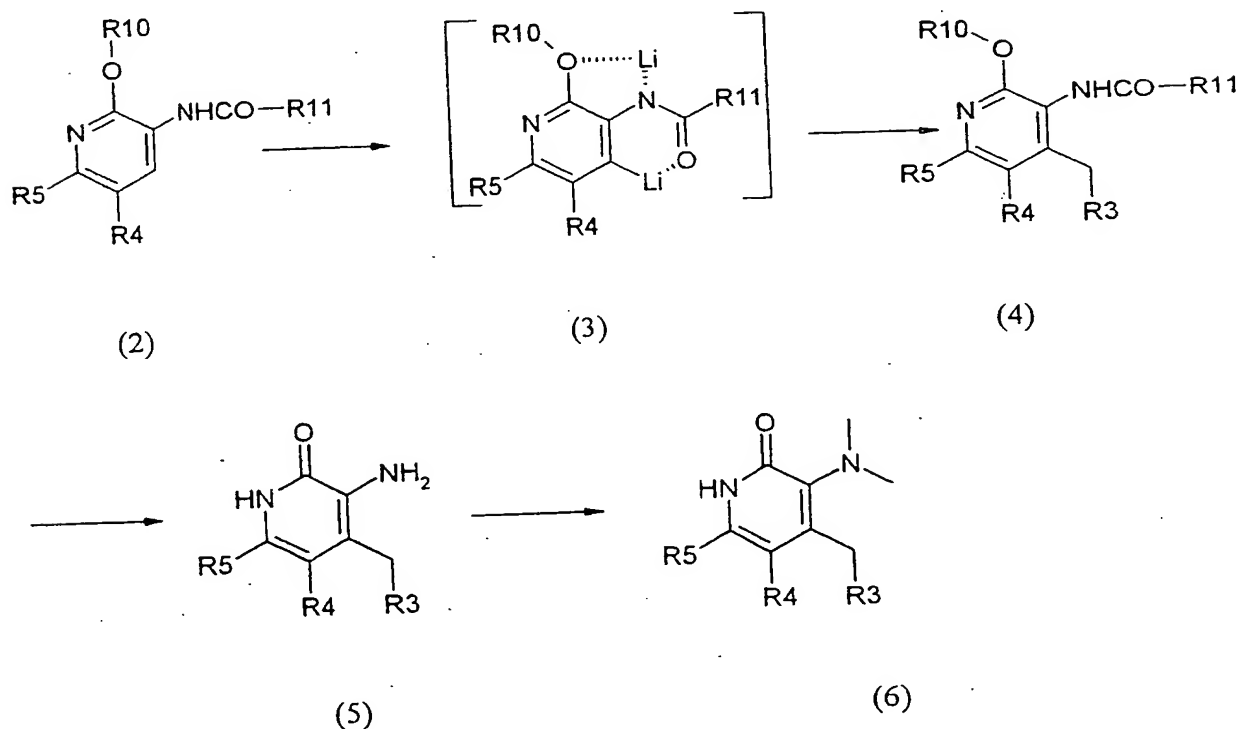
c) obtaining the pyridinone (4) by reacting the organocopper reagent with optionally substituted benzyl halide.

d) hydrolysing the protected pyridinone (4) and obtaining the deprotected pyridinone (5).

5 e) substituting the 3-amine group of the pyridinone (5) and obtaining the pyridinone (6).

This first process is summarized in the reaction Scheme I hereinafter:

**SCHEME I**



In this process  $R_{10}$  and  $R_{11}$  represent independently  $C_1-C_6$  alkyl. In a preferred embodiment,  $R_{10}$  is a methyl group and  $R_{11}$  is a tert-butyl group.

The  $C_1-C_6$  alkyllithium, reacted with the pyridine(2) can be a n-butyllithium.

5 The optionally substituted benzyl halide used in the step c) is preferably benzyl bromide.

The hydrolysis of the protected pyridinone(4), resulting in its deprotection, is advantageously obtained by adding hydrochloric acid to the pyridinone(4) and refluxing the mixture.

10 In a preferred embodiment, the amino group in position 3 of the pyridinone ring, deprotected during the step (d) is substituted by alkylation, by the Eschweiler-Clarke reaction.

Compounds wherein X represents  $-(CH_2)_q-Z-(CH_2)_r-$ , Y represents O,  $R_3$  is an optionally substituted phenyl group and  $R_6$  is an hydrogen atom  
15 can be obtained by a similar process.

Compounds wherein X represents C (= O), or  $-CH_2-$ , Y represents O,  $R_3$  is an optionally substituted phenyl group and  $R_6$  is an hydrogen atom can be obtained by a second process.

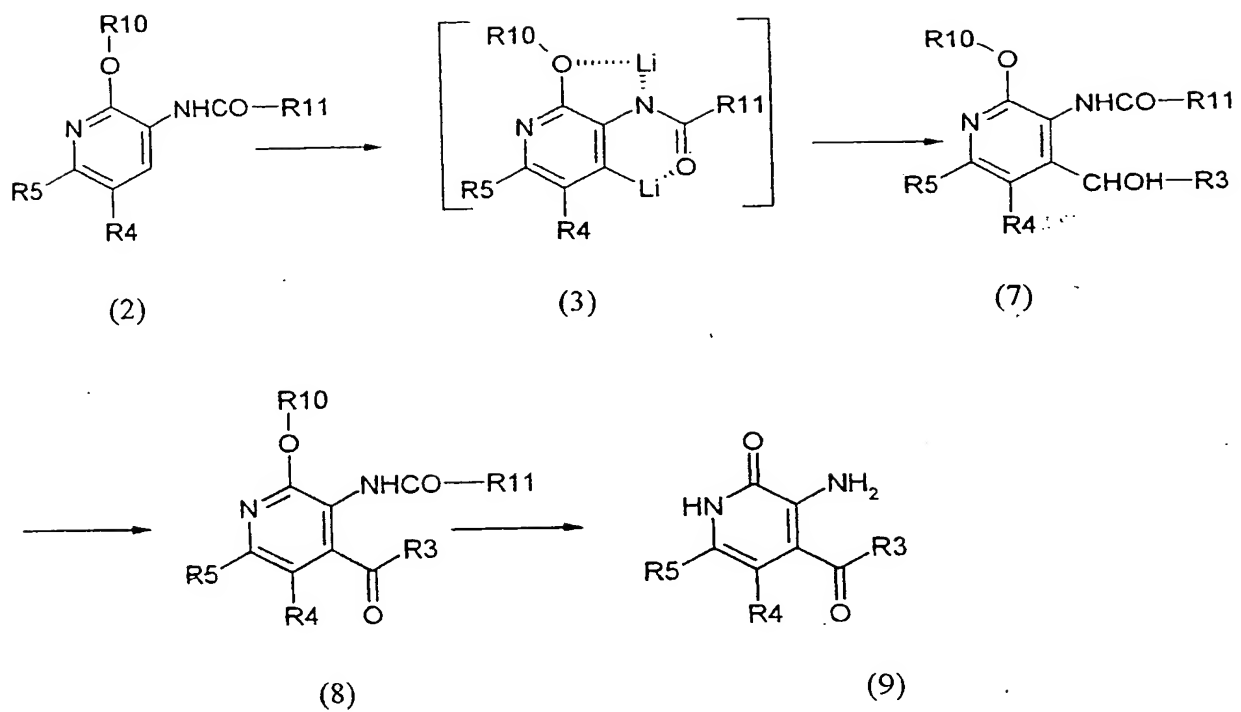
20 In this second process, the lithiated derivative (3) is reacted with an optionally substituted benzaldehyde, resulting in the intermediates of formula (7).

The intermediate (7) is oxidized to intermediate (8).

The intermediate (8) is thereafter deprotected by hydrolysis, as in the first process, resulting in the pyridinone (9) of general formula I.

25 This second process is summarized in the reaction scheme II hereinafter.

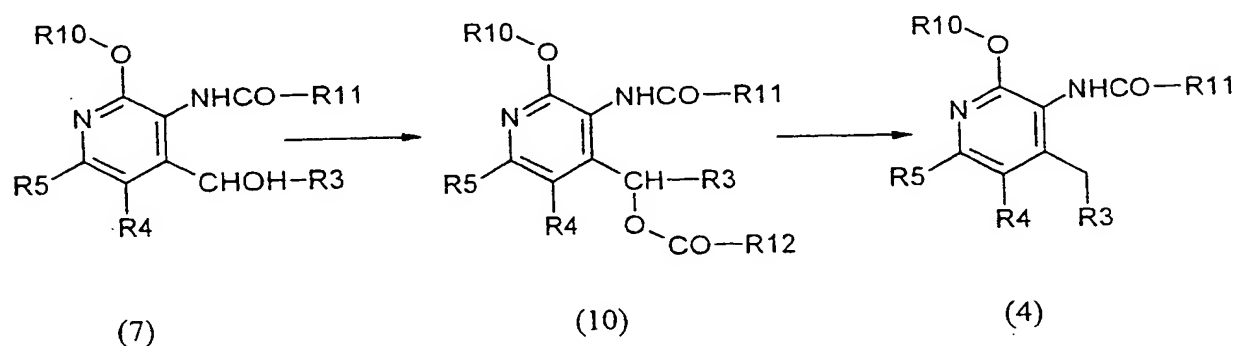


Reaction scheme II

Preferably the oxidation of the intermediate (7) is performed in the presence of manganese dioxide.

The intermediate (7) can also be transformed into corresponding ester (10) wherein  $R_{12}$  represents a  $C_1$ - $C_4$  alkyl group whose hydrogenolysis provides pyridinone(4) in better yields. Preferably, the ester (10) wherein  $R_{12}$  is  $CH_3$  is prepared by treatment of intermediate (7) with acetic anhydride. Subsequently hydrogenolysis is performed under hydrogen atmosphere and in the presence of a catalyst, especially 30% paladized charcoal. This process is summarized in the reaction scheme III

### Reaction scheme III



Other compounds of general formula I, and wherein X is  $(CH_2)_p$  or  $(CH_2)_q$ -Z- $(CH_2)_r$  or C(=O), and  $R_3$  is other than phenyl and  $R_6$  is other than hydrogen can be obtained by these processes, appropriately adapted by the man skilled in the art.

The compounds according to the present invention, in which X is S can be obtained by the process described in the article of DOLLE et al. (1995, previously cited) or in the corresponding patent application WO 97/05 113, the contents of which are included in the present application.

The compounds can also be obtained by other processes known by the man skilled in the art.

The present invention relates moreover to the intermediates of the processes hereabove disclosed. In particular it relates to the lithiated  
5 derivative of formula (3).

The compounds of the present invention are useful in the inhibition of HIV reverse transcriptase, and in particular HIV-1 reverse transcriptase and the prevention or treatment of infection by the human immuno deficiency virus (HIV) and of HIV-related diseases , such as AIDS.

10 For these purposes, the compounds of the present invention may be administered orally, parenterally (including sub-cutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles.

15 Thus, another object of the present invention is a method, and a pharmaceutical composition for treating HIV related diseases, HIV infection, and in particular AIDS.

The invention relates also to these compounds for use as medicine and to their use for the manufacture of a medicine for the  
20 treatment of HIV related diseases, HIV infection, and in particular AIDS.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets, nasal sprays, sterile injectable preparations, or suppositories.

The present invention is illustrated without being limited by the  
25 following examples.

**EXAMPLES:****EXAMPLE 1**

**Preparation of 3-dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one.**

**1) 5-Ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine.**

This compound has been prepared as indicated by DOLLE et al. (1997, Tetrahedron, vol.53, n°37, 12.505-12.524). The content of this article is hereby incorporated by reference.

3,68g of 3-Amino-5-ethyl-2-methoxy-6-methylpyridine (22,14 mmol), obtained as indicated by HOFFMAN et al. (1993, J. Med. Chem., 36, 953-966), was dissolved in a mixture of dichloromethane (260 ml) and triethylamine (3.39 ml). The mixture was cooled at 0°C and 3.00 ml of trimethylacetyl chloride was added dropwise. The solution was stirred at 0°C for 15 min. and then washed with 100 ml water. The aqueous layer was extracted with 3 x 200 ml dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane as eluant to provide the 5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (5.31g; 96%). Elemental analysis calculated for C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>; C, 67.17; H, 8.86; N, 11.19; O, 12.78; found : C, 67.11; H, 8.56; N, 10.91; O, 12.67.

**2)4-(3,5-Dimethylbenzyl)-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine**

i) By lithiation of 5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine:

5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine and 3,5-dimethylbenzyl bromide were dried in the presence of phosphorus pentoxide under vacuum at room temperature during 24 hours. Copper iodide ( $\text{Cu}^{\text{I}}$ ) was dried in the presence of phosphorus pentoxide under vacuum at 50°C for 24 hours. 5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (1.06g) and freshly distilled tetramethylethylenediamine (TMEDA) (2.24 mL) were dissolved in dry tetrahydrofuran (THF) (26 mL) and the mixture was cooled at -78°C under a nitrogen atmosphere. n-Butyllithium (1.6 M in hexane, 9.26 mL) was added dropwise. The mixture was stirred for 1 hour at 0°C.

$\text{Cu}^{\text{I}}$  :dimethyl sulfide complex, prepared by adding dimethylsulfide (14 mL) to a suspension of copper iodide (2.82g) in dry THF (52 mL) at -78°C under  $\text{N}_2$  atmosphere, was then added dropwise to the mixture at -78°C. The mixture was stirred at 0°C for 30 min and cooled again at -78°C to allow the addition of 3,5-dimethylbenzyl bromide (3.81g) dissolved in THF (4 mL). The resulting mixture was stirred at 0°C for 3 hours and at room temperature for 12 hours. 16 mL of water and 20 mL of 28% aqueous ammonium hydroxide were added. The aqueous layer was extracted with 3 x 80 mL of ether. The combined organic layers were washed with 40 mL of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:0 to 8:2) as eluant giving 4-(3,5-dimethylbenzyl)-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (577 mg, 37%) mp 138-139°C.

ii) By hydrogenolysis of  $\pm$  (5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridin-4-yl)-(3,5-dimethylphenyl)-methyl acetate.

(+, -) (5-Ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridin-4-yl)-  
(3,5-dimethylphenyl)-methylacetate.

8.34g of (+, -)-(3,5-dimethylphenyl)-(5-ethyl-2-methoxy-6-methyl-3-  
5 pivaloylaminopyridin-4-yl)-methanol, prepared as described below, was  
dissolved in pyridine (200 mL) and added to acetic anhydride (10.24 mL),  
and the solution was stirred for 1.5 h at room temperature and for 60 h at  
60°C. An additional 10.24 mL of acetic anhydride (108.51 mmol) was added  
and heating was continued at 60°C for 24 h. The pyridine was evaporated  
10 under reduced pressure and the residue was taken up in 500 mL of ethyl  
acetate. The organic layer was washed with 170 mL of an aqueous  
saturated sodium bicarbonate solution, 170 mL of water and 170 mL of  
brine, dried over magnesium sulfate and the solvent was evaporated. The  
residue was purified by column chromatography using dichloromethane-  
15 ethanol (1:0 to 95:5) to give the titled compound (8.78g, 95%) mp 70-71°C.

A mixture of this compound (850 mg) and Pd-C (30%, 850mg) in  
acetic acid-water-dioxane (42.5 mL, 2:1:2, v/v/v) was stirred at room  
temperature for 24 hours under 10 atm of hydrogen. The catalyst was  
removed by filtration and washed with ethanol. The solvent of the combined  
20 filtrates was evaporated under reduced pressure giving 4-(3,5-  
dimethylbenzyl)-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (726  
mg, 99%) which was identical to the compound as prepared in example  
1.2.i).

25 3) 3-Amino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one.

3M aqueous hydrochloric acid (150 mL) was added to a  
suspension of 4-(3,5-dimethylbenzyl)-5-ethyl-2-methoxy-6-methyl-3-  
pivaloylaminopyridine (2.36 g) in water (300 mL). The mixture was refluxed

for 3.5 h and then stirred at room temperature for 12 h. The solution was basified by adding concentrated ammonium hydroxide and was extracted with 3 x 800 mL ethyl acetate. The combined organic layers were washed with 110 mL brine, dried over magnesium sulfate and concentrated under reduced pressure giving 3-amino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one . (1.79g, 100%). mp 204-205°C.

4) 3-Dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2-(1H)-one .

To a stirred solution of 3-amino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one (200 mg) and 37% of aqueous formaldehyde (0.60 mL) in 5 mL of acetonitrile was added 139 mg of sodium cyanoborohydride. Glacial acetic acid (0.07 mL) was added dropwise and the reaction mixture was stirred at room temperature for 2 hours. An additional 0.07 mL of glacial acetic acid was added, and stirring was continued for 30 minutes. The solvent was evaporated and 15 mL ether were added to the resulting residue. The organic layer was washed with 3 x 30 mL 1N aqueous potassium hydroxide and 3 mL brine, dried over magnesium sulfate and concentrated under reduced pressure to give 3-dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one (200 mg, 91%) mp 229-230°C.

EXAMPLE 2: 1) Biological activity of the compound according to example 1.

1. Material and Methods

The antiviral activity, the expression and purification of the recombinant HIV-RT enzyme, the reverse transcriptase activities and the inhibition of RT were evaluated as described in WO 97/05 113.

The retrovirucidal effect and the reverse transcription were measured as described hereinafter.

### 1.1. Retrovirucidal effect.

5

HIV-1 viral suspensions were obtained by coculture of MT4 cells and H9 cells chronically infected by HIV-I<sub>Lai</sub> isolate. 200µl of a cell supernatant containing viral particles (HIV-I<sub>Lai</sub>: 100 TCID<sub>50</sub>) were incubated at room temperature with various concentrations of different inhibitors. After  
10 3 hours, virions were washed through 0.02µm anopore membrane in 1.5 mL Vectaspin tube (Whatman) for 10 minutes at 5 000 g . Each of the three subsequent washes was performed in the same conditions after the viral concentrate was refilled with 500 µL of RPMI medium. Then, the viral concentrate was readjusted to the initial volume with RPMI plus 10% foetal  
15 calf serum (FCS). The residual infectivity was assayed on P4 cells as described by CHARNEAU et al.. (1994, J. Mol. Biol., 241, 651-662). Briefly, P4 cells were plated using 100 µL of DMEM medium plus 10% FCS in 96 plate multi-wells at  $20 \times 10^5$  cells per mL. After overnight incubation at 37°C, the supernatant was discarded and the viral preparation (200 µL) was  
20 added. One day later the wells were washed three times in PBS. Each well was refilled with 200 µL of a reaction buffer containing 50 mM Tris-HCl pH 8.5, 100 mM 2-mercaptoethanol, 0.05% Triton X-100 and 5 mM 4-methylumbelliferyl β-D-galactopyranoside (MUG). After 3 hours at 37°C, the level of the reaction was measured in a fluorescence microplate reader.

25



## 1.2) Reverse transcription.

The plasmid pAV4 containing the 50-997 HIV-1 nucleotide fragment (MAL strain) in pSP64, under the control of the bacteriophage T7 promoter was a kind gift from Dr. J.L. DARLIX (INSERM-Lyon, France). E. coli HB 101 recA<sup>-</sup> was used for plasmid amplification. After digestion of this clone with PstI and in vitro transcription using T7 RNA polymerase, a HIV-1 genomic RNA fragment starting at position +50 of the MAL sequence was obtained. In vitro transcription using T7 RNA polymerase as performed as follows. Three µg of linearized plasmid DNA were transcribed in 100 µL of 40 mM Tris -HCl pH 8.0, 8 mM MgCl<sub>2</sub>, 10 mM spermidine, 25 mM NaCl, 10 mM dithiothreitol, 0.5 mM of each ribonucleoside triphosphate, with 100 units of T7 RNA polymerase and in the presence of 20 units of human placenta ribonuclease inhibitor, for 2 hours at 37°C. After treatment with 12 units of Rnase-free Dnase I (for 10 minutes at 37°C), the RNA transcripts were extracted with 1 volume of phenol/chloroform/isoamyl alcohol (24:24:1) and with chloroform and precipitated in 2.5 volumes of ethanol and 0.3 M ammonium acetate (pH 5.5).

Reverse transcription was performed in a total volume of 50 µL containing 50 mM Tris-HCl pH 8.0, 6 mM MgCl<sub>2</sub>, 2 mM dithiothreitol, 12 mM NaCl, 150 nM HIV-1 RNA, and either 200 nM of a synthetic oligodeoxynucleotide primer (18-mer ODN) complementary to the PBS of HIV-1 RNA, or 200 nM tRNA<sup>Lys3</sup>. When the 18-mer ODN was used as primer, incubation was carried out at 37°C with the template and 300 nM RT. After 30 minutes, 10 µCi [α-<sup>32</sup>P]dGTP (3000 Ci/mmol) and 0.1 mM of each dNTP were added and the incubation proceeded for 30 minutes at 37°C. With tRNA<sup>Lys3</sup> as primer, the same conditions were used except that tRNA and RNA were prehybridized by heating for 2 minutes at 90°C and then slowly cooled. Samples were extracted with phenol-chloroform and

collected by ethanol precipitation. Reaction products were analyzed on 8% polyacrylamide-TBE (90 mM Tris pH 8.3, 90 mM borate, 2 mM EDTA)-7 M urea gels.

## 5 RESULTS

The antiviral activity of the compounds according to example 1 has been tested on various strains.

On HIV-LAI wild type this compound shows the following activities:  
10  $IC_{50} = 0,2nM$ ;  $CC_{50} > 10^5 nM$  (S.I.  $> 33.333$ ).

On an HIV-1 novirapine resistant strain the activities of the compound of example 1 are as follows:

$$IC_{50} > 10^4 nM$$

$$CC_{50} > 10^4 nM$$

15 The compound of example 1 has been also tested on various HIV strains and primary cell cultures. The table 1 illustrates the activity of this compound on these strains.

The retrovirucidal effect of the compound according to example 1 has been tested. Table 2 illustrates this effect at various doses of this  
20 compound.

The  $IC_{50}$  of the compound of example 1 for the inhibition of the reverse transcriptase is 20 nM.

**TABLE 1-Anti HIV-1 activity of the compound of  
example 1 on various HIV strains and primary cell cultures**  
**IC<sub>50</sub>(nM)/CC<sub>50</sub>(nM)**

Compound	HIV-1 IIIIB /MT4	HIV-1 AZTres. /MT4	HIV-1 IIIIB /PBMC	HIV-2 D 194 /PBMC	HIV-1 Bal/ Mono/macro- phages
Example 1	2.4/>1000	0.2/>1000	0.58/>1000	>1000/> 1000	0.004/>1000

5

**TABLE 2: Inhibition of infectivity of the compound of  
example 1**

Dosage of compound of example 1	% inhibition of infectivity
10 nM	26%
100 nM	46%
1 µm	83%
10 µm	99%

10 **EXAMPLE 3: Other 3-(amino- or aminoalkyl) pyridinone derivatives and  
their retrovirucidal activity against two different HIV-1 strains.**

**3.1 Compounds:**

15 Further compounds according to the general formula (I)  
(compounds n°1-25, 27-108, 110-125, 127-145 and 147-203) as well as four  
intermediate compounds used for synthesis (compounds n°26, 109, 126 and  
146) have been synthesized and are listed in table 3 below.

The meaning of each of the groups Y, Q and R3 - R6 is defined for  
every exemplified pyridinone derivative.

### 3.2 RETROVIRUCIDAL EFFECT

The retrovirucidal effect of each pyridinone derivative listed in table  
3 has been assayed according to the teachings of example 2, excepted that  
the anti-viral effect has been tested on the two following HIV-1 strains:

- a) HIV-1 strain IIIB (see example 2);
- b) HIV-1 strain 103 N which is a mutant strain bearing a point  
mutation in the reverse transcriptase gene leading to an enzyme wherein the  
initial Lys-103 residue is replaced for a Asn residue.

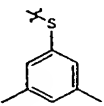
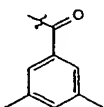
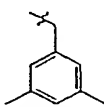
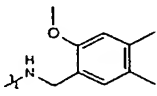
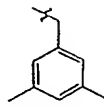
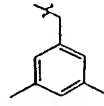
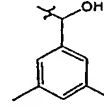
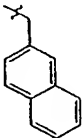
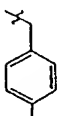
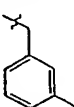
HIV-1 103N strain exhibits resistance to the reverse transcriptase  
inhibitor TIBO R82913 (BALZARINI J. et al. 1993, Virology, 192: 246-253).  
The HIV-1 103 N strain has also been described by SAHLBERG et  
al., (1998, Antiviral Res., 37 (3) : ASS) and BALZARINI et al. (1996,  
Antimicrobial Agents and Chemotherapy, 40 (6): 1454-1466).

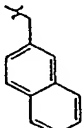







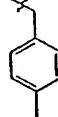
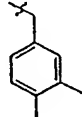
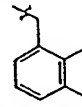
The results are expressed as  $pIC_{50}$  ( $pIC_{50} = -\log IC_{50}$ ), of every of  
compound as regards to each of the HIV-1 strains IIIB and 103N. Thus, the  
 $pIC_{50}$  value of compound n°1 as regards to HIV-1 IIIB being 7,6999, the  $IC_{50}$   
can be directly deduced as being equal to  $10^{-7,6999}M$ .


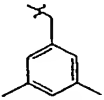
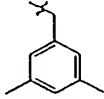
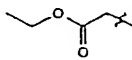
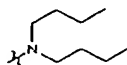
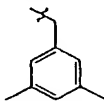
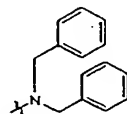
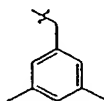

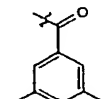
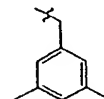
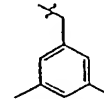
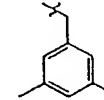

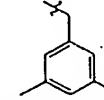
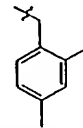
Such high retrovirucidal activities had never been observed  
previously when using prior art reverse transcriptase inhibitors.

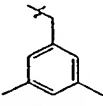
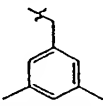
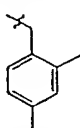
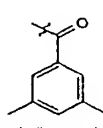

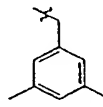
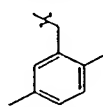
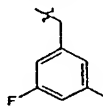
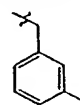
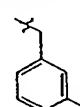
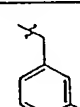
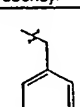
Consequently, the novel pyridinone derivatives according to the  
present invention are of a high therapeutical value against HIV related  
diseases, particularly against HIV-1 related diseases.

TABLE 3

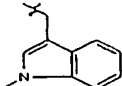

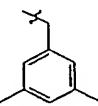
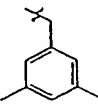

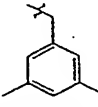
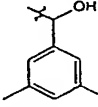
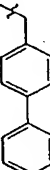
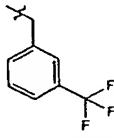
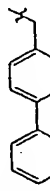
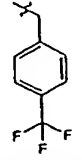
	Y	O	R3	R4	R5	R6	HIV1 pIC50	
							strain IIB	strain 103R
1	O	NH2		Et	Me	H	7.699	6.671
2	O	NH2		Et	Me	H	6.612	6.64
3	O	NMe2		Et	Me	H	8.004	7.438
4	O			Et	Me	H	5.094	<4
5	O	NH2		Et	Me	H	6.261	5.636
6	O	NH2		Et	Me	H	5.795	5.026
7	O	NH2		Et	Me	H	<4	<4
8	O	NH2		Et	Me	H	4.373	4.39
9	O	NH2		Et	Me	H	5.373	5.103

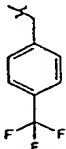
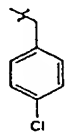
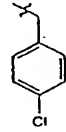

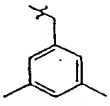
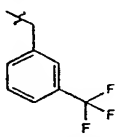
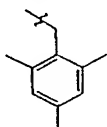
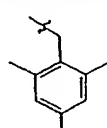
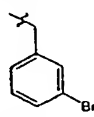
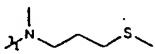
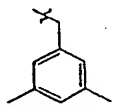
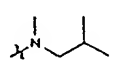
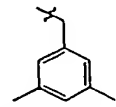
10	o	NMe2	 Chemistry 82	Et	Me	H	6.241	4.389
11	o	NMe2	 3,5-Dimethylbenzyl	Et	Me	Me	7.215	6.094
12	o	NEt2	 3,5-Dimethylbenzyl	Et	Me	H	8.022	6.363
13	o	NMe2	 3-Methylbenzyl	Et	Me	H	8.824	7.622
14	o	NMe2	 2-Methylbenzyl	Et	Me	H	7.676	5.849
15	o	NH2	 3,5-Dimethylbenzyl	H	H	H	<4.17	4.138
16	o	NMe2	 3,5-Dimethylbenzyl	H	H	H	5.061	4.401
17	o	N(n-Pr)2	 3,5-Dimethylbenzyl	Et	Me	H	6.285	4.379
18	o	NMe2	 4-Methylbenzyl	Et	Me	H	6.454	4.895
19	o	NMe2	 3,4-Dimethylbenzyl	Et	Me	H	7.447	5.947
20	o	NMe2	 2,3-Dimethylbenzyl	Et	Me	H	6.926	5.585

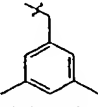
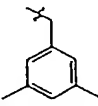
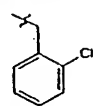
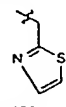
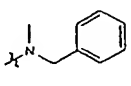
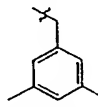
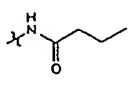
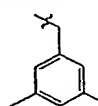
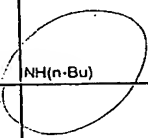
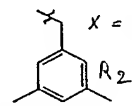
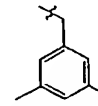

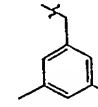
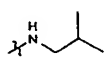
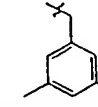
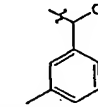
21	O	NMe2		Et	Me	H	8.409	6.65
22	O	NMe2		Et	Me	Benzyl	4.603	<4
23	O	NMe2		Et	Me	 Chemistry 163	5.254	<4
24	O	 Chemistry 165		Et	Me	H	4.262	<4
25	O	 Chemistry 171		Et	Me	H	<4	4.259
26	O	 Chemistry 177		Et	Me	H		
27	O	NH2		Me	Et	H	5.949	5.098
28	O	NMe2		Me	Et	H	8.032	6.943
29	O	NHCH2Ph		Et	Me	H	6.555	5.496
30	O	 Piperidin-1-yl		Et	Me	H	6.214	4.224
31	O	NH2		Et	Me	H	<4	<4

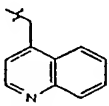
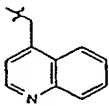
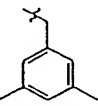
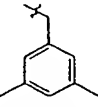
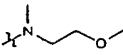
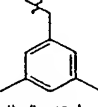

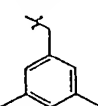
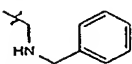
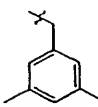

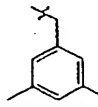
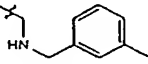
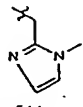
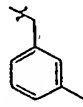
32	o	NH <sub>2</sub>		Mo	Me	H	6.104	<5
33	o	NMe <sub>2</sub>		Me	Me	H	8.42	6.286
34	o	NMe <sub>2</sub>		Et	Me	H	5.019	<4
35	o	NMe <sub>2</sub>		Et	Me	H	8.585	7.987
36	o	 N-Morpholino		Et	Me	H	6.763	<4
37	o	NMe <sub>2</sub>		Et	Me	H	6.796	5.729
38	o	NMe <sub>2</sub>		Et	Me	H	8.155	7.402
39	o	NH <sub>2</sub>		Et	Me	H	5	4.751
40	o	NMe <sub>2</sub>		Et	Me	H	8.585	7.412
41	o	NH <sub>2</sub>		Et	Me	H	5.131	4.473
42	o	NMe <sub>2</sub>		Et	Me	H	8.569	7.18

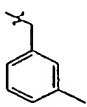
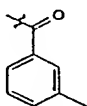
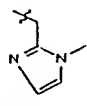
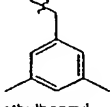
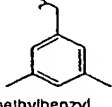
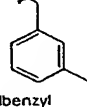
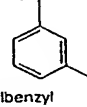
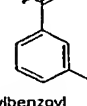
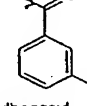
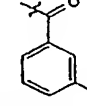
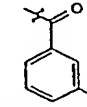
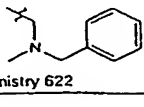


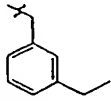
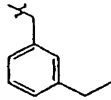
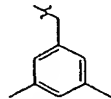
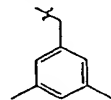
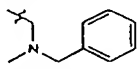
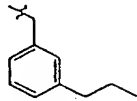
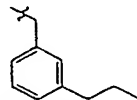
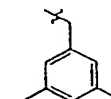
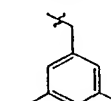
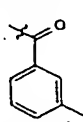
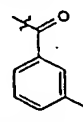
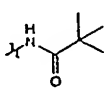
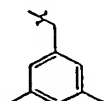
43	O	NMe2	 Chemistry 280	Et	Me	H	7.377	6.422
44	O	NMe2	 Chemistry 286	Et	Me	H	7.889	6.355
45	O	NMe2	 3,5-Dimethylbenzyl	Et	Me	Et	5.519	4.095
46	O	NHMe	 3,5-Dimethylbenzyl	Et	Me	H	8.119	7.034
47	O	 Chemistry 303	 3,5-Dimethylbenzyl	Et	Me	H	7.767	6.968
48	O	NMe2	 Chemistry 310	Et	Me	H	8	6.711
49	O	NH2	 Chemistry 316	Et	Me	H	<4	<5
50	O	NH2	 3-Trifluoromethylbenzyl	Et	Me	H	<5	<5
51	O	NMe2	 Chemistry 334	Et	Me	H	5.384	<5
52	O	NH2	 4-Trifluoromethylbenzyl	Et	Me	H	<4	<5

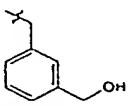
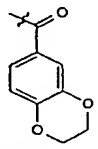
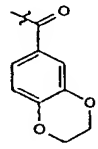
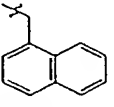
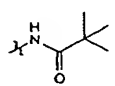
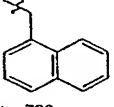
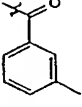

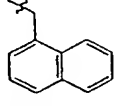
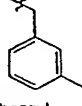
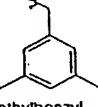
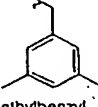
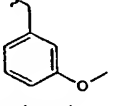
53	o	NMe2		Et	Me	H	5.828	<5
54	o	NH2		Et	Me	H	<4	<5
55	o	NMe2		Et	Me	H	6.651	
56	o	 Chemistry 363		Et	Me	H	8.194	7.11
57	o	NMe2		Et	Me	H	8.086	6.414
58	o	NH2		Et	Me	H	<4	<5
59	o	NMe2		Et	Me	H	5.029	<5
60	o	NMe2		Et	Me	H	8.444	7.001
61	o	 Chemistry 393		Et	Me	H	7.693	5.922
62	o	 Chemistry 399		Et	Me	H	6.604	5.305

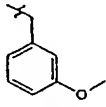
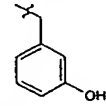
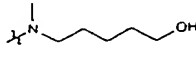
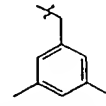
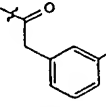
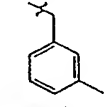
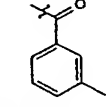
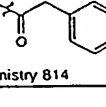
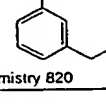
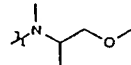
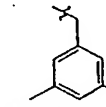
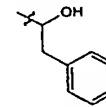
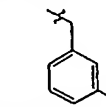
63	O	NMe <sub>2</sub>		Me	n-Pr	H	7.029	6.334
64	O	NHC(=O)-iPr		Et	Me	H		
65	O	NMe <sub>2</sub>		Et	Me	H	8.284	6.405
66	O	NMe <sub>2</sub>		Et	Me	H	7.588	5.72
67	O	 Chemistry 435		Et	Me	H	6.804	4.955
68	O	 Chemistry 441		Et	Me	H		
→ 69	O	$R_1$  NH(n-Bu)	$X = CH_2$ 	Et	Me	H	6.891	5.655
70	O	NMe <sub>2</sub>		 Chemistry 45	Me	H	7.752	7.159
71	O	NMe <sub>2</sub>		n-Pr	Me	H	7.777	7.049
72	O	 Chemistry 465		Et	Me	H	7.079	<4
73	O	NH <sub>2</sub>	 Chemistry 472	Et	Me	H	8.027	6.92

74	o	NH <sub>2</sub>	 Chemistry 478	Et	Me	H	<4	<4
75	o	NMe <sub>2</sub>	 Chemistry 490	Et	Me	H	5.252	4.132
76	o	NH <sub>2</sub>	 3,5-Dimethylbenzyl	H	i-Am	H	<5.494	<4
77	o	NMe <sub>2</sub>	 3,5-Dimethylbenzyl	H	i-Am	H	5.827	<4
78	o	 Chemistry 507	 3,5-Dimethylbenzyl	Et	Me	H	8.678	7.128
79	o	 Chemistry 513	 3,5-Dimethylbenzyl	Et	Me	H	6.987	5.47
80	o	NH <sub>2</sub>	 Chemistry 520	Et	Me	H	<4	<4
81	o	NHEt	 3,5-Dimethylbenzyl	Et	Me	H	7.866	6.444
82	o	 Chemistry 531	 3,5-Dimethylbenzyl	Et	Me	H	7.735	5.813
83	o	NH <sub>2</sub>	 Chemistry 538	Et	Me	H	<4.033	<4
84	o	NH <sub>2</sub>	 Chemistry 544	Et	Me	H	<4	<4
85	o	NH <sub>2</sub>	 3-Methylbenzyl	Me	Me	H	4.954	<4


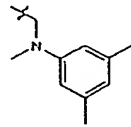
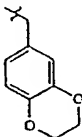
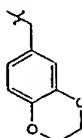
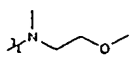
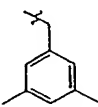
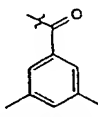
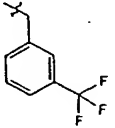
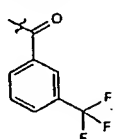
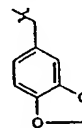
86	O	NMe <sub>2</sub>		Me	Me	H	7.863	5.936
87	O	NH <sub>2</sub>		Et	Me	H	6.46	5.653
88	O	NMe <sub>2</sub>		Et	Me	H	<4	
89	O	NH <sub>2</sub>		H	n-Bu	H	6.237	
90	O	NMe <sub>2</sub>		H	n-Bu	H	6.359	
91	O	NH <sub>2</sub>		(CH <sub>2</sub> ) <sub>4</sub>	(CH <sub>2</sub> ) <sub>4</sub>	H	5.73	
92	O	NMe <sub>2</sub>		(CH <sub>2</sub> ) <sub>4</sub>	(CH <sub>2</sub> ) <sub>4</sub>	H	7.807	
93	O	NMe <sub>2</sub>		Et	Me	H	8.721	
94	O	NH <sub>2</sub>		Me	Me	H	5.153	
95	O	NEt <sub>2</sub>		Et	Me	H	8.268	
96	O	NMe <sub>2</sub>		Me	Me	H	7.824	6.37
97	O	NH <sub>2</sub>		Et	Me	H	<4	<4

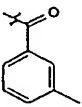
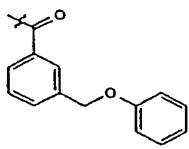
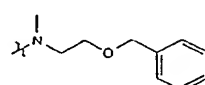
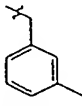
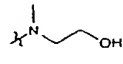
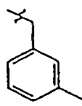

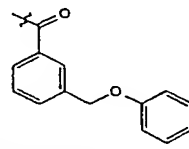
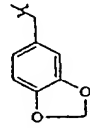
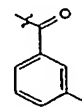
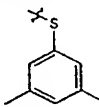
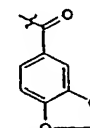
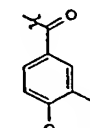
98	O	NH <sub>2</sub>		Et	Me	H	5.358	4.978
99	O	NMe <sub>2</sub>		Et	Me	H	8.569	6.718
100	O	NH <sub>2</sub>		H	Me	H	4.871	<4
101	O	NMe <sub>2</sub>		H	Me	H	6.341	4.25
102	O	NMe <sub>2</sub>		Et	Me	H	4.369	<4
103	O	NH <sub>2</sub>		Et	Me	H	5.747	
104	O	NMe <sub>2</sub>		Et	Me	H	8	7.058
105	O	NH <sub>2</sub>		Cl	H	H	4.943	
106	O	NMe <sub>2</sub>		Cl	H	H	7.063	
107	O	NMe <sub>2</sub>		(CH <sub>2</sub> ) <sub>4</sub>	(CH <sub>2</sub> ) <sub>4</sub>	H	7.231	
108	O	NMe <sub>2</sub>		Me	Et	H	7.005	
109	O			H	OMe	H		



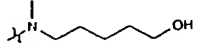

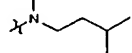

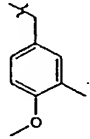
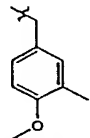



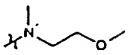
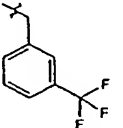
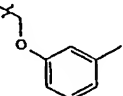
110	o	NMe2		Chemistry 706	Et	Me	H	7.783	
111	o	NH2		Chemistry 712	Et	Me	H	<4	
112	o	NMe2		Chemistry 718	Et	Me	H	6.394	
113	o	NH2		Chemistry 724	Et	Me	H	5.273	
114	o		Chemistry 730		Et	Me	H		
115	o	NMe2		3-Methylbenzoyl	Et	Me		Chemistry 745	<4.307
116	o	NMe2		Chemistry 748	Et	Me	H	6.627	
117	o	CH2NMe2		3-Methylbenzyl	(CH2)4	(CH2)4	H	<4.139	
118	o	NH2		3,5-Dimethylbenzyl	Me	i-Pr	H	4.042	
119	o	NMe2		3,5-Dimethylbenzyl	Mo	i-Pr	H	6.114	
120	o	NH2		3-Methoxybenzyl	Et	Me	H	5.033	

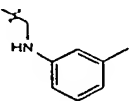
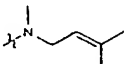
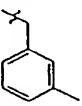
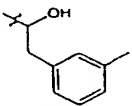
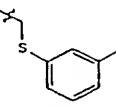
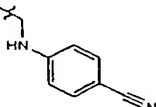
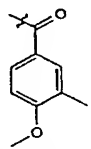
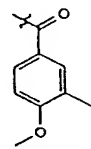
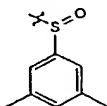
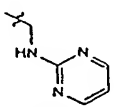
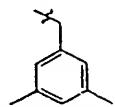
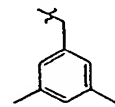
121	O	NMe2		Et	Me	H	8.469	6.948
122	O	NMe2		Et	Me	H	7.196	
123	O	 Chemistry 789		Et	Me	H	8.444	6.918
124	O	NH2		Et	Me	H	4.389	
125	O	NHCHO		Et	Me	H		
126	O	NHCHO		Et	Me	H		
127	O	NMe2		Et	Me	H	4.174	
128	O	NMe2		Et	Me	H	7.848	
129	O	 Chemistry 825		Et	Me	H	8.398	7.057
130	O	NH2		Et	Me	H	<4	
131	O	NH2		(CH2)3	(CH2)3	H	5.799	

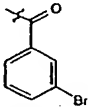
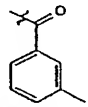
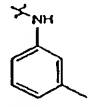
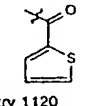
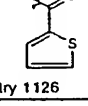
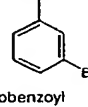
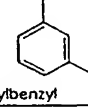
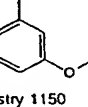
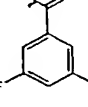
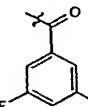
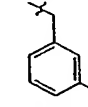



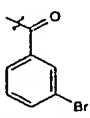
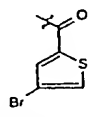
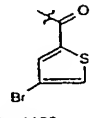
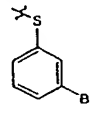
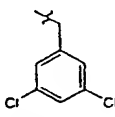
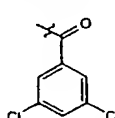
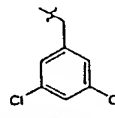
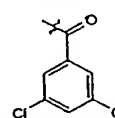
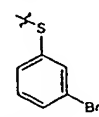
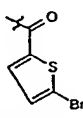
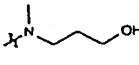
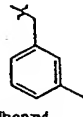
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133	O	NMe2		Et	Me	H	4.94	
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135	O	NMe2		Et	Me	H	6.688	
136	O		3-Methylbenzyl	Et	Me	H	9	6.996
137	S	NMe2		Et	Me	H	7.658	
138	S	NMe2		Et	Me	H	8.215	7.401
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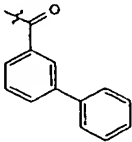
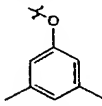
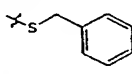
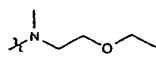
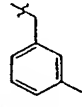
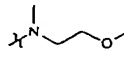
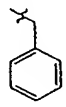
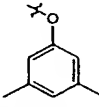
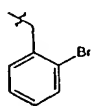
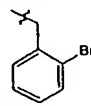
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152	O	NMe2		Et	Me	Ph	4.21	
153	O	NMe2		Et	Me	NH2	6.749	
154	O	 Chemistry 981		Et	Me	H	8.009	6.262
155	O	 Chemistry 987		Et	Me	H	7.514	
156	O	NH2		Et	Me	H	4.934	
157	O	NMe2		Et	Me	H	6.413	
158	O	NMe2		Et	Me	H	8.041	6.625
159	O	NH2		Et	Me	H	7.011	
160	O	NMe2		Et	Me	H	8.678	7.177
161	O	 Chemistry 1023		Et	Me	H	7.821	5.814
162	O	NMe2		Et	Me	H	6.418	5.026

163	O	NMe2		Chemistry 1036	Et	Me	H	5.596	4.236
164	O			3-Methylbenzyl	Et	Me	H	7.818	6.505
165	O	NMe2		Chemistry 1048	Et	Me	H	4.354	<4
166	O	NMe2		Chemistry 1054	Et	Me	H	5.693	4.518
167	O	NMe2		Chemistry 1060	Et	Me	H	6.338	5.828
168	O	NH2		Chemistry 1066	Et	Me	H	4.525	4.806
169	O	NMe2		Chemistry 1072	Et	Me	H	7.101	5.771
170	O	NMe2		Chemistry 1078	Et	Me	H	8.553	7.224
171	O	NMe2		Chemistry 1084	Et	Me	H	5.895	4.74
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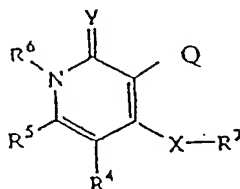
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177	O	NH2		Et	Me	H	5.106	<4
178	O	NMe2		Et	Me	H	7.873	6.461
179	O	NHMe		Et	Me	H	8.42	7.182
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181	O	NMe2		Et	Me	H	7.928	
182	O	NH2		Et	Me	H	5.933	
183	O	NMe2		Et	Me	H	8.481	
184	O	Chemistry 1167		Et	Me	H	8.523	6.804

185	O			Et	Me	H	8.745	7.433
186	O	NH <sub>2</sub>		Et	Me	H	5.781	
187	O	NMe <sub>2</sub>		Et	Me	H	8.481	7.006
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191	O	NMe <sub>2</sub>		Et	Me	H	8.097	7.553
192	O	NMe <sub>2</sub>		Et	Me	H	8.699	8.319
193	O	NMe <sub>2</sub>		Et	Me	H	8.481	7.245
194	O	NH <sub>2</sub>		Et	Me	H	4.665	
195	O			Et	Me	H	8.569	6.52

196	O	NMe2		Chemistry 1240	Et	Me	H	6.411	
197	O	NH2		Chemistry 1246	Et	Me	H	7.307	
198	O	NH2		Chemistry 1252	Me	H	H	4.457	
199	O			3-Methylbenzyl	Et	Me	H	7.924	
200	O			Benzyl	Et	Me	H	8.42	5.95
201	O	NMe2		Chemistry 1276	Et	Me	H	8.585	7.231
202	O	NH2		2-Bromobenzyl	Et	Me	H	5.715	
203	O	NMe2		2-Bromobenzyl	Et	Me	H	8.161	

## CLAIMS:

1. A compound having the formula (1)



wherein:

- Q represents -NR<sub>1</sub>R<sub>2</sub> or -R<sub>0</sub>NR<sub>1</sub>R<sub>2</sub> wherein:

\*R<sub>0</sub> represents C<sub>1-6</sub> alkanediyl;

\* R<sub>1</sub> and R<sub>2</sub> each independently represent C<sub>1-6</sub>alkyl or C<sub>3-6</sub>alkenyl; said C<sub>1-6</sub>alkyl and C<sub>3-6</sub>alkenyl may be substituted with one, two or three substituents selected from hydroxy, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkylthio, aryloxy, arylthio, amino, mono- or di(C<sub>1-4</sub>alkyl)amino and aryl; or

\* R<sub>1</sub> and R<sub>2</sub> taken together may form a bivalent radical -R<sub>1</sub>-R<sub>2</sub>- wherein -R<sub>1</sub>-R<sub>2</sub> - represents -(CH<sub>2</sub>)<sub>2</sub>-O-(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-NR<sub>7</sub>-(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-CH(NHR<sub>7</sub>)-(CH<sub>2</sub>)<sub>2</sub>- or -(CH<sub>2</sub>)<sub>n</sub> wherein R<sub>7</sub> represents hydrogen or C<sub>1-4</sub>alkyl and n represents 2, 3, 4, 5 or 6;

- R<sub>3</sub> represents aryl or a monocyclic or bicyclic heterocycle selected from pyridinyl, pyrimidinyl, thiazolinyl, furanyl, thienyl, imidazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl; said monocyclic or bicyclic heterocycle may optionally be substituted with one, two or three substituents each independently selected from hydroxy, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, halo, trifluoromethyl, dimethylenoxy or phenyl,

-R<sub>4</sub> and R<sub>5</sub> each independently represent hydrogen, C<sub>1-6</sub>alkyl,

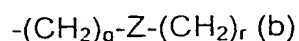


C<sub>3-6</sub>alkenyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl, amino, mono- or di(C<sub>1-4</sub>alkyl) amino, formyl, C<sub>1-4</sub>alkylcarbonyl carboxyl, C<sub>1-4</sub> alkyloxycarbonyl, or C<sub>1-4</sub>alkyl aminocarbonyl; wherein C<sub>1-6</sub>alkyl and C<sub>3-6</sub>alkenyl may be substituted with one, two or three substituents selected from hydroxy, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkyl  
 5 thio, aryloxy, arylthio, amino, mono- or di(C<sub>1-4</sub>alkyl)amino and aryl; or R<sub>4</sub> and R<sub>5</sub> taken together form a bivalent radical of formula -R<sub>4</sub>-R<sub>5</sub>-wherein -R<sub>4</sub>-R<sub>5</sub>- represents -CH=CH-CH=CH- or -(CH<sub>2</sub>)<sub>t</sub>, wherein t represents 3 or 4;

- R<sub>6</sub> represents hydrogen, hydroxy, C<sub>1-4</sub>alkyloxy, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>alkenyl, aryl, C<sub>1-4</sub>alkyl, amino, mono- or di(C<sub>1-4</sub>alkyl)amino or alkylaryl;

10 - Y represents O or S;

- X represents a radical of formula:



wherein p represents 1, 2, 3, 4 or 5;

15 q represents 0, 1, 2, 3, 4 or 5;

r represents 0, 1, 2 or 3;

- Z represents NR<sub>8</sub>, C(=O), CHOH, CHNR<sub>8</sub>R<sub>9</sub>, CF<sub>2</sub>, O, S or CH=CH; wherein R<sub>8</sub> and R<sub>9</sub> each independently represent hydrogen or C<sub>1-4</sub> alkyl;

20 or

a N-oxide, a stereochemically isomeric form or a pharmaceutically acceptable addition salt thereof.

2. A compound according to claim 1 wherein R<sub>1</sub> and R<sub>2</sub> represent each a methyl group.

25 3. A compound according to claim 1 wherein X represents -CH<sub>2</sub>- and R<sub>3</sub> represents a phenyl group substituted with two methyl groups.

4. A compound according to claim 1 which is the 3-dimethylamino-4-(3,5-dimethylbenzyl)-5-ethyl-6-methylpyridin-2(1H)-one.

5. A process for the obtention of compounds according to claim 1 wherein X represents  $-\text{CH}_2-$ , Y represents O,  $\text{R}_3$  is an optionally phenyl group substituted and  $\text{R}_6$  is hydrogen comprising the following steps:

a) reacting a pyridine, substituted in position 2 with an alkoxy group and in position 3 with an amidoalkyl group, with a  $\text{C}_1$ - $\text{C}_6$  alkyllithium, resulting in a lithiated derivate of the said pyridine.

b) transforming said lithiated derivate into an organocopper reagent by reacting it with a complex formed by Cu I and dimethyl sulphide.

c) obtaining a protected pyridinone by reacting the organocopper reagent with optionally substituted benzyl halide.

d) hydrolysing said protected pyridinone and obtaining a deprotected pyridinone.

e) substituting the amine-3 group of said deprotected pyridinone and obtaining the desired pyridinone compound.

6. A process for the obtention of compounds according to claim 1 wherein X represents  $-\text{C}(=\text{O})$ , Y represents O,  $\text{R}_3$  is an optionally substituted phenyl group, and  $\text{R}_6$  is hydrogen wherein:

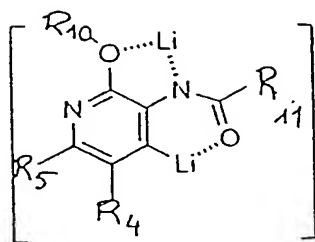
a) reacting a pyridine, substituted in position 2 with an alkoxy group and in position 3 with an amidoalkyl group, with a  $\text{C}_1$ - $\text{C}_6$  alkyllithium, resulting in a lithiated derivate of said pyridine.

b) reacting the lithiated derivative with an optionally substituted benzaldehyde, resulting in a substituted pyridinone,

c) oxidizing said substituted pyridinone, resulting in a protected pyridinone,

d) deprotecting said protected pyridinone by hydrolysis, resulting in the desired pyridinone compound.

7. Lithiated derivative having the following formula :



5

wherein  $R_4$  and  $R_5$  are as defined in claim 1, and  $R_{10}$  and  $R_{11}$  are independently  $C_1$ - $C_6$  alkyl.

8. Pharmaceutical compositions comprising a therapeutically effective amount of at least a compound according to claim 1 and pharmaceutical carriers.

9. Method of treatment of HIV-related diseases comprising the administration of an effective amount of a compound according to claim 1.

10. Method of treatment of HIV-infection comprising the administration of an effective amount of a compound according to claim 1.

15

## INTERNATIONAL SEARCH REPORT

Int ernational Application No

PCT/EP 99/03023

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/73 A61K31/44 C07F1/02 C07D213/74 C07D213/75  
C07D417/06 C07D401/06 C07D405/06 C07D409/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 05113 A (CENTRE NAT RECH SCIENT ;BISAGNI EMILE (FR); DOLLE VALERIE (FR); NG) 13 February 1997 (1997-02-13) cited in the application claims; examples	1-10
A	EP 0 462 800 A (MERCK & CO INC) 27 December 1991 (1991-12-27) cited in the application claims	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document, but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

27 July 1999

Date of mailing of the international search report

05/08/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
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Fax: (+31-70) 340-3016

Authorized officer

Bosma, P

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 03023

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9 and 10  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 9 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 99/03023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9705113 A	13-02-1997	FR 2737496 A EP 0843663 A	07-02-1997 27-05-1998
EP 0462800 A	27-12-1991	AU 641769 B AU 7845291 A CA 2044828 A FI 912925 A JP 2079995 C JP 4253961 A JP 7107051 B NZ 238576 A PT 98003 A US 5308854 A	30-09-1993 19-12-1991 19-12-1991 19-12-1991 09-08-1996 09-09-1992 15-11-1995 22-12-1994 31-08-1993 03-05-1994